OUTLINE

"Registries for Evaluating Patient Outcomes"

AHRQ Task Order: 290-05-0035-1

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Chapter 1. Introduction

Overview

The introduction will present the structure and objectives of the reference document or handbook. It will explain that the goal of the handbook is to provide a variety of stakeholders in both the public and private sectors with information that they can use to guide the design and implementation of patient registries, the analysis and interpretation of registry data from patient registries, and the evaluation of registry design, operation, and interpretation.

This section will provide a working definition of a registry for the purposes of the document and provide a taxonomy of the major types of registries, including product registries (drug, device, vaccine), health care service registries (procedure, encounter), and broader disease-based registries. It will also describe the range of purposes for which patient registries are used, such as observing the natural history of a disease and its treatment(s), assessing or monitoring real-world safety and effectiveness, determining the value or appropriate reimbursement level for a product or procedure, and assessing quality of care and provider performance.

This introductory chapter will also describe the emerging role of registries and the variety of areas where they are currently being utilized. Finally, it will compare and contrast what can be learned from registries as compared to clinical trials.

- Purpose and overview of the reference document

  This reference is devoted to observational programs that are designed to serve a predetermined clinical, scientific, or policy purpose, and which use highly structured, clinical data systematically collected close in time to their occurrence.

  This reference concentrates on registries created for the purpose of examining clinical and comparative effectiveness, with an understanding that this encompasses the balancing of benefits and harm, including safety. Recognizing that registries can serve multiple purposes, this document also addresses registries that describe natural history, as well as those that examine cost effectiveness and quality measurement and improvement.

- Registry definition(s) and taxonomy

  This reference will address a broad range of registries including those that aim for total ascertainment, as well as those that utilize samples of convenience for longitudinal cohort-type studies.

- Uses of registries for evaluating patient outcomes
- Overview of the epidemiologic principles, scientific framework, and methodologies for designing registries that collect observational data to answer specific scientific questions

- Strengths and limitations of the observational data captured by registries as compared to the data required for experimental research, including clinical trials

SECTION I. CREATING A REGISTRY

This section will cover the major steps in the process of establishing a registry. It includes chapters regarding planning, design, selection of data elements and data sources, and issues of ethics, governance, data ownership, and privacy.

Chapter 2. Planning a Registry

Overview

This chapter will describe the recommended steps in planning a registry, from a needs assessment to balancing scientific inquiry and financial constraints. The chapter will describe the factors that should be considered when deciding whether to establish a registry, such as the availability and quality of existing information on the subject in question, the cost versus benefit of a registry compared to other options, the feasibility of implementation in real-world practice, the financial sustainability, and governance etc.

- Guiding principles such as limiting burden, maximizing relevance and value to all stakeholders, and keeping it simple
- Determining the goals and objectives of the registry
- Answering key questions, including: Is a registry the best option to achieve those goals? What type of registry is most suited to the goals? Is it relevant to the key stakeholders and feasible to implement in clinical practice?
- What is the cost versus benefit of implementing a registry versus other options?
- Use of feasibility testing and/or pilot data in the planning process
- Governance

Defining goals

- What are the primary purpose(s)?
    - Clinical effectiveness and comparative effectiveness, including safety as well as natural history, cost-effectiveness, and quality measurement / improvement.
- Who are the stakeholders and potential users of the information?
    - Physicians

        - Professional Societies
        - Academics
    - Public
        - General
        - Advocacy groups
        - Individual patients
    - Payers/Employers/Insurers
    - Government
    - Certifiers or Accreditors
    - Pharmaceutical drug and device manufacturers
- Is there a need?
    - What types of information or other registries already exist and what are their limitations?

What should be done?

- Defining an overall purpose for the specific registry
- Defining the target population
- Determining the patient outcome(s) of greatest importance
- Defining the scope (setting, geography, size, etc.) based on the purpose
- Creating parameters for the study design (refer to chapter 3)

What can be done? (Considering budgets and funding sources)

- Major cost elements/drivers
    - Start-up costs (Design, setup and recruitment)
    - Operational cost drivers
        - Personnel costs
            - Study personnel
            - Expert consultants (biostatisticians, epidemiologists, database experts, subject matter experts, etc.)
            - Advisory boards and committees
        - System and process costs
            - E-transmission: computers
            - Fax
            - Mail/overnight (less attractive)

    - Site and patient cost drivers
        - Legal costs
        - Institutional Review Board costs
        - Healthcare costs (if applicable)
        - Incentives/compensation costs
            - Site personnel
        - Patients incentives (if applicable)
        - Investigator community costs (e.g. meetings)
- Potential sources of funding
    - Government
    - Industry
    - Foundation
    - Private
    - Professional Society

Planning for governance and study execution

- Assembling a multidisciplinary team
    - Subject matter experts
    - Database experts
    - Computer Scientists
    - Epidemiologists
    - Biostatisticians
    - HIPAA experts
- Governance
    - Internal vs. external
    - Roles and responsibilities of external oversight committees
        - What are the needs/roles?
            - Provide expert guidance on design and conduct; assure ethical and scientific integrity; provide stakeholder representation; construct rules for publications and data use; assist in recruitment, etc.
        - Types of oversight committees
            - Advisory boards
            - Publications and data use committees

- Data safety monitoring boards
    - When might these be required?
- IRB's, ethics and privacy boards
- Other

- Determining data access/data use during and following the registry

Chapter 3. Registry Design

Overview

This chapter will describe general design considerations, including how to define a scientific question within a registry. It will address important practical questions, such as: how to observe real-world practice without influencing it, strategies for collecting information on small but important subgroups, and what is feasible to accomplish within the constraints of registries? How do you address and evaluate issues such as provider/patient relevance, respondent burden, and loss to follow-up? The chapter will also consider the desirability and feasibility of using consistent data definitions to maximize the opportunities for data integration and aggregation. These concepts will be presented in a manner that takes into account cost considerations as well as scientific aims. Guidance documents will be identified, including "Development and Use of Risk Minimization Action Plans" (March, 2005), "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (March, 2005), "Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies" (April, 2005), and "Establishing Pregnancy Exposure Registries" (August, 2002).

Reason why registry is being created

As with any credible scientific study, there should be a clearly articulated study question(s) or objective(s) that ultimately drives the rationale for the study design, analysis, and conduct. This rationale should include enough background information about the motivation for the registry to help the reader gain the necessary perspective on study design and analysis choices.

These reasons fall into a few general types to identify and 'track' people:

- With a particular disease/outcome (these are person-focused)
    - Examples: cancer, rare disease, chronic diseases, QoL, utilization, for recruitment pool for clinical trials, disease natural history, pregnancy
- With a particular exposure (these are product-focused)
    - Examples: general surveillance, pregnancy registries for particular drugs; environmental or workplace exposures, medication/device exposures, diet; there are some potentially questionable applications including providing 'experience' in the use of the product

- Who belong to a particular **population segment** (these are demographically-focused)
    - Examples: twin registries, occupational classes, geographic locus (i.e., to study health services or needs), membership (Latter Day Saints), population registries (i.e., Olmsted County), gender
- During a specific **absolute time period** or birth cohort (these are 'time-focused')
    - examples: birth cohorts
- As part of a program evaluation, disease management effort, quality improvement, or controlled distribution for drugs with serious safety profiles (e.g., Accutane®, clozapine) where the participants in the registry are identified because of their participation in a particular program

These reasons will also determine the appropriateness of the design and analysis. A registry can be specifically designed to be descriptive or to address an analytic question.

Types of registry designs to consider: advantages and disadvantages

- Retrospective vs. prospective
- Patient centered vs. clinician centered
    - Data obtained from patient only
    - Data obtained from clinician only
    - Data obtained from both clinician and patient
    - Adding data from other sources, such as health insurances claims data and National Death Index
- Comparator vs. not
- Electronic data capture/linkage/record abstraction vs. from clinician vs. from patient
- Designs nested within registries
    - Case-control
    - Case-cohort
    - Cross-sectional

Patient inclusion/exclusion

Very clear definitions necessary, documented in protocol including rationale for inclusion and exclusion criteria.

Comparison group

- Internal

- External
- Historical
- No comparison group

Sampling strategies for patient identification

- Sampling strategies
    - Probability sampling
        - Simple random sampling
        - Stratified sampling
        - Systematic sampling
        - Cluster (area) sampling
        - Multistage sampling
    - Non-probability sampling
        - Accidental, haphazard, convenience
        - Modal instance
        - Purposive
        - Expert
        - Quota
        - Snowball
        - Heterogeneity sampling
    - "Total" ascertainment
- Recruitment
- Need for representativeness: This depends on the purpose and kind of inference needed, e.g., for understanding biological effects, it is not necessary to sample in proportion to the underlying distribution in the population, whereas representativeness is important when the goal is to estimate prevalence rates for policy decisions.

See also recruitment/identification

Provider/user/institution identification

The recruitment should be driven in part by how representative the investigators want to be, the sampling strategy, and how important that is to the overall validity of the study.

- Volunteer vs. solicited
- Recruitment of patients through physicians
- Recruitment of patients directly

- Working through professional organizations (physician and patient advocacy) to encourage participation
- Reimbursement and incentives to participate
- How many sites will be included? If multi-site, how much standardization will be enforced across sites
- Patient and provider recruitment and management [refer to chapter 7]

Bias

- External vs. Internal Validity Considerations
- Threats to validity
    - Selection bias
    - Channeling bias
    - Loss to Follow-up
    - Recruiting experienced users vs. novices

Practical logistics

- Key skills involved in designing study
    - Clinical expertise
    - Design expertise
    - Statistical expertise
- Burden on patient
- Burden on clinician
- Key skills involved in implementing study [refer to Chapter 2]
    - Project coordination
    - Communication
    - Validation and Oversight

Oversight structures

- Oversight committee
- Data safety monitoring board

Role of participating clinicians and patients

- Design
- Receipt of interim and final data

Chapter 4. Data Elements for Registries

Overview

This chapter will address key groupings of data elements that are important for registries, including options for the use of personal identifiers (and associated trade-offs), key demographic descriptors, and key categories of information to be considered (e.g., disease of interest, "exposure" data (drug, device, vaccine, etc.), co-morbidities or essential elements of a health history), etc. It will discuss issues of burden, validity, and reliability in the selection of data elements, composite scales, or patient-reported outcomes instruments. The chapter will also consider the desirability and feasibility of using consistent data definitions in order to maximize the opportunities for data integration and aggregation. To this end, the chapter will review data harmonization issues that need to be considered in selecting data elements and definitions and the availability of certain standards that should be used when feasible (e.g., coding dictionaries for diseases and medical encounters (ICD-9), procedures (CPT), safety reporting (MedDRA®), prescription medications (NDC), injectibles, etc.).

What domains need to be quantified to accomplish the purpose of the registry, including examples of clinical data standards (e.g., LOINC, ICD-9, MedDRA® (safety), WHODRUG)

- Reasons to select data elements
- To identify outcomes
- To create important subsets
- To adjust for confounding
- To predict outcomes
- To understand sources of bias
    - Propensity scores (see chapter 9)
    - Imputation

Select data elements to capture that domain

- Common data definitions are the first step. [Please comment on structured data elements]
- Do clinical data standards exist? (if so, use them!)
- Is the patient-centered outcome valid, reliable, responsive, interpretable, translated

- Discuss issue of patient identifiers -> raises privacy issues further covered in chapter 6.
- Regarding PHI
    - Tracking PHI requires informed consent
        - Since some patients refuse, it introduces bias
        - Should attempt to collect some data so that you can adjust for observable bias
    - Advantages of PHI include
        - Ability to follow patients longitudinally
        - Ability to link to other data
        - Remove issues of double-counting
    - De-identified data, e.g. HealthFacts
- Each registry should have a data map
    - Identifies source of all data (see chapter 5)
    - Identifies how they will be integrated
    - Defends the validity/reliability of the data
    - Should be an integral component of data management plan

Select from the available elements identified, those that you want to incorporate

- Include additional measures, if necessary
- Emphasize use of common data definitions to allow merging of data elements (e.g., 1=male, 2=female)

Pilot test the feasibility of the data collection tools

- Time to complete – subject/abstractor burden
    - Highly burdensome elements may be collected in a subset (nested registry)
- Missing data rate - completeness
- Test-retest correlations and agreement
- Test completeness and quality of the source data element

Begin data collection

Chapter 5. Other Data Sources for Registries

Overview

This chapter will describe the types of data that are included in registries and describe how data can be collected from different entities, including patients, providers, pharmacists, insurers, and laboratories. The chapter will describe how data from existing sources, such as other patient registries, administrative claims databases, electronic health records, death indices, and census data can and cannot be used and integrated into a new registry.

Data sources:

- Strengths and weaknesses and appropriate use of the data from the different sources
- Validity and reliability issues (link to discussions in Section 4, Data Elements)
- Challenges with linking primary and secondary data
- Primary
    - Prospective – healthcare provider, patient, etc.
    - Chart abstraction
- Secondary
    - Administrative claims databases
    - Laboratory databases
    - Electronic health records
    - Death indices (NDI, SSI)
    - Census data
    - Existing registries
    - Industry databases (e.g., safety surveillance, product registration)

Data management

- Essential to map out all data elements and sources
- How will the data be managed coming in from different sources?
    - What is integrated or linked, when and how?
    - Data standards, common definitions, units of measure, etc.? Do we have data element library defining each data element? Need for transformation of data, etc.?
    - How to ensure maintenance of linkage to the appropriate patient (common unique identifier is the ultimate goal, but may not start out that way as data comes in)

Logistics

This section will describe the process and challenges related to obtaining access to the data and interface with data source owners.

- Legal agreements for data access, use, and ownership (refer to chapter 6)
- PHI issues – to access data and to link data on same patient coming from different sources, etc.
- Process or management agreements early on: roles/responsibilities for access and transfers, schedules, etc.
- Systems compatibility, testing transfers

Chapter 6. Principles of Registry Ethics, Data Ownership, and Privacy

Overview

This chapter will review ethical considerations of registries, the roles and responsibilities of internal and external oversight committees, and the importance of registry transparency. It will also explain legal concepts regarding ownership and use of registry data and privacy regulations as they apply to registries.

Introduction

- Legal information is based on US law
- Issues addressed here refer to registries in general and are not focused on types of studies (e.g. where registries are linked to the collection of genetic material) that may have additional requirements or considerations. In such cases, the reader will be referred to more specific references on those topics.

Considerations of Registry Types for Ethical, Privacy, and Regulatory Protections

- Case examples used to help describe various types

Privacy and Confidentiality

- Legally Mandated Registry Reporting vs. Non-mandated Registries
- Data collection issues, including research participant protections, the Office of Human Research Protections (OHRP), and the Privacy Act (HIPAA and OCR)
- HIPAA-exempt vs. HIPAA; status as "covered entity" under Privacy Rule; Special rules for data submitted to FDA
    - Identify the HIPAA exclusions
    - If HIPAA affected, how registry can be developed (e.g. data use and business associate agreements, authorization)

- Related issues
    - Options for patients consenting into registries; authorization must include each purpose of use or disclosure or be general enough to cover all anticipated uses
    - Hands off – no interest vs. stakeholders with heavy involvement — expresses ends of continuum
    - Anonymized vs. non-anonymized; aggregated vs. non-aggregated; coded with link to identifiers; control of link/code; audit; use of dates; patient monitoring
    - Population-based vs. non-population based; authorization and waiver
    - Government vs. non-government use of registry information; data as public record
    - Populations needing special ethical considerations
        - Children
        - Mentally incompetent
        - Meeting legal competency criteria
- Research with human subjects – Common Rule Application as it applies to human subjects as they enter a registry [keep general]
    - Disease vs. Exposure (Iatrogenic, drug, device) registry
    - Industry vs. Academia; federal jurisdiction under FWA irrespective of funding
    - Identifiable private information "readily ascertained" by investigator; coded private information; audit; consent and waiver
    - Confidentiality of institutional identities?
- Data ownership
    - Trace the legal landscape that is emerging related to ownership and involvement as it specifically related to registries (if different)
    - Issues related to Subpoenas for data: relation to undermining protection guarantees in data collection for registry; certificates of confidentiality
    - Data ownership issues, including who "owns" healthcare data entered into registries at the level of the patient, the site, and the aggregate data repository
- Institutional Review Boards
    - Role of IRBs (and/or Privacy Boards) with respect to registries. Are there any situations when IRB review is not required (e.g., quality improvement/healthcare operations)?
    - Certificates of Confidentiality

- Use case studies/models to demonstrate points

Registry transparency — are there differences between registries and clinical trials?

- Basis for public release of information on registries
    - Applicability of registers (e.g. clinicaltrials.gov)
    - Variance in requirements for registries vs. clinical trials

SECTION II. OPERATING REGISTRIES

This section will cover all steps in the process of operating a registry. This section will include chapters about provider and patient recruitment, data collection and quality assurance, and the analysis and interpretation of registry data.

Chapter 7. Provider and Patient Recruitment and Management

Overview

This chapter will discuss strategies for recruiting providers and will address potential pitfalls associated with different strategies. This chapter will also describe strategies for maximizing patient recruitment and retention in a registry, including the potential role of incentives such as payments and personalized health reports. Specific topics include the following:

Provider recruitment and retention

- Understanding the needs and interests of potential participants
- Recruitment strategies, such as partnering with professional associations, using recruitment seminars, targeting high prescribers and treatment specialists, etc.
- Techniques for maximizing enrollment, such as using broad inclusion and limited exclusion criteria
- Procedural challenges to recruitment (e.g., contracting, document collection), privacy concerns, participation costs
- Strategies for maximizing provider retention and ways to increase the value of registries for participating providers
- Cost of provider recruitment and appropriate remuneration for participation

Patient recruitment and retention

- Understanding the needs and interests of potential participants
- Patient recruitment issues and procedural challenges, including informed consent and explanation of risks
- Patient retention goals and issues, including what is a reasonable follow-up period? What is a reasonable follow-up rate? When does retention compromise validity?
- Patient incentives, including different types of incentives and the ethical, legal, or study validity issues to be considered with patient incentives
- Costs of patient recruitment and retention

Partnerships as recruitment tools

- Government agencies (AHRQ, etc.)
- Physician professional association endorsements (ACC, AMA, etc.)
- Patient advocacy groups endorsements (MDA, etc.)
- Nonprofit foundations (e.g., RWJ)
- Industry (Pharma, etc.)
- Partnerships may be sources of financial support?

Recruit providers from your sample frame, which depends on the purpose of your registry. i.e., what population do you want to describe?

- Health systems (HMO, etc.)
- Hospitals
- Physicians
- Patients

Hospitals, physicians and patients can be selected randomly, consecutively or as a convenience sample. [Refer to chapter 3]

Physicians who manage only a few patients per year with the disease that is the subject of your registry are less likely to be interested in enrolling their patients than physicians who see many such patients, unless the disease is rare or ultra rare, in which case the registry may be of great interest.

True population-based sampling is challenging to achieve in a voluntary registry. Most registries will enroll a convenience sample of hospitals and physicians and consecutive sample of eligible patients from these sampling frames. [Refer to chapter 3 for sample size and sampling techniques]

Understand the focus of this registry; then proceed to develop a strategy to recruit these individuals or hospitals. [Refer to chapter 2, Planning]

- How many subjects can you afford to enroll?
- What incentives can you offer?
    - Modest financial reimbursement
    - Access to data
    - Compliance with regulatory mandates

Methods of hospital recruitment

- AHA database of US hospitals
- Use sales representatives of drug or device companies to suggest hospitals
- Enroll hospital through physicians who work there and are interested in your registry
- State or county lists of licensed hospitals
- Other

Methods of physician recruitment

- Mailing lists purchased from physician specialty organizations
- Use sales representatives of pharma to suggest physicians
- Ask opinion leaders in the field to suggest colleagues who might be interested
- Other

Methods of patient recruitment

- MD office
- Hospital wards
- Telephone survey
- Letter survey

Procedural considerations as they relate to recruitment

- Contracts with sponsors, hospitals, and physicians
- Ethical review and approval
- IRB costs are often over $1,000 per hospital
- Confidentiality – for hospitals, physicians, patients

Support services that can aid retention of patients and providers

- Websites
- Newsletters
- Telephone helpline
- Instruction manuals
- Training meetings
- Site audit/retraining visits
- Customer satisfaction/opinion surveys
- Regular data reports to stake holders

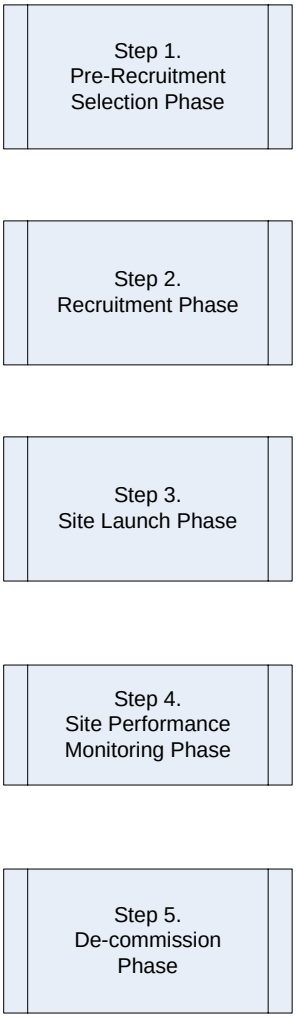
Vetting hospitals and physicians

- By hospital characteristics (e.g. bed size, geographic location, etc.)
- By MD characteristics (e.g. specialty training, etc.)
- Volume of target cases per year
- Availability of a study coordinator on local MD or hospital staff
- Availability of computer facilities (internet connectivity)
- Practice environment (HMO, private practice, etc.)

Pitfalls in recruitment and retention and practical suggestions for minimizing problems

- Biases in hospital and MD recruitment (MDs invite their friends, disease experts invite other disease experts, etc.)
- Biases in patient recruitment (older and more seriously ill patients may be excluded due to challenges in enrolling and following up)

Proposed model for registry site/organization recruitment



Each site / organization may go through steps 1 and/or 2 to establish interest and feasibility to participate in an outcomes registry.

Step 1: Pre-recruitment considerations

- Does a site/organization meet the inclusion criteria for the registry (see section on "Vetting hospitals and physicians")?
- Do they have an adequate sample size of cases?
- Do they have necessary resources to support insertion of data into the registry (personnel or electronic data transfer structures)?
- Are there barriers to contracts or IRB issues that are so significant as to impede a reasonable timeframe to recruit a site?

Step 2: Recruitment phase

- During this phase all points under the "Procedural considerations" section need review as part of the feasibility assessment and final agreement to participate in the registry
- If a site or institution is deemed eligible then the subsequent 3 steps or phases may occur

Step 3: Site launch phase

- "Support services that can aid in the retention of providers and patients" section needs to be addressed. This could include but are not limited to:
    - Instruction manuals (paper/online)
    - Training meetings

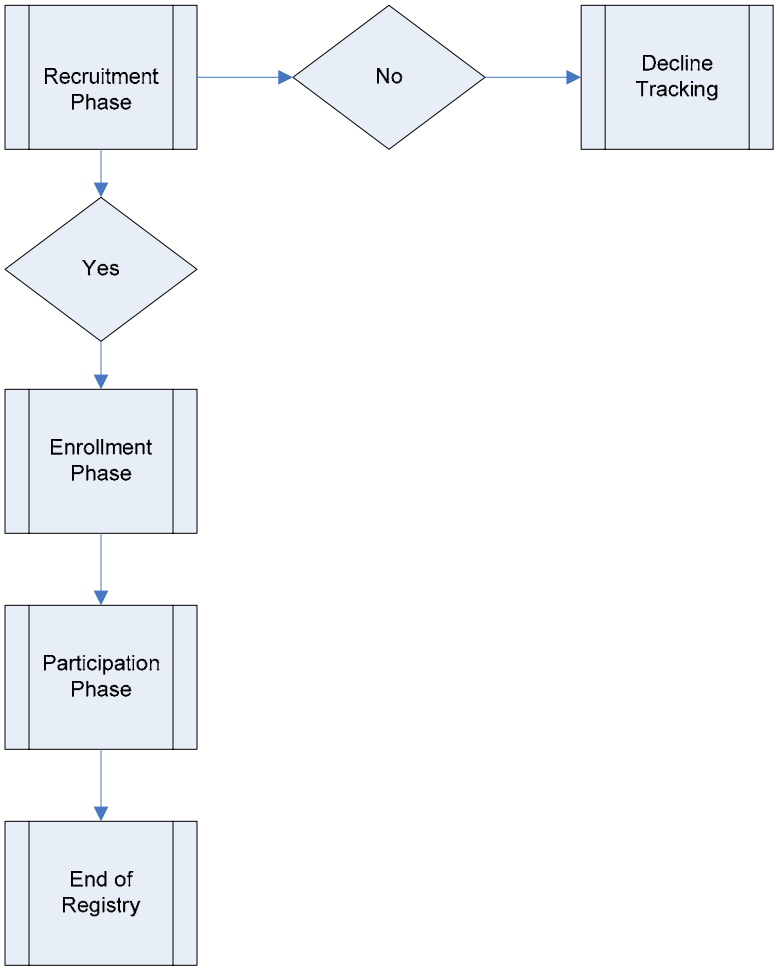
Step 4: Site performance monitoring phase

- Onsite audit visits or remote review for data validation purposes and quality assurance monitoring. This may necessitate the need for retraining to the abstraction model for common data elements

Step 5: De-commission phase

- At the conclusion of a registry there may be a need to decommission a site/organization. This could take the form of a final report, site visit for final chart review, or a final investigators meeting, etc.

Proposed model for patient recruitment and retention in a registry



Step 1: Recruitment phase

- In the recruitment phase, necessary source documents such as the 'Dear Patient' letter of recruitment should be written to accommodate varying levels of health literacy.
- If the patient declines, is there a need to track the reason for decline and some delimited demographic and clinical characteristics descriptors so as to understand the generalizabiltiy of research findings?
- Will the registry track the proportion of acceptors vs. decline patients?

Step 2: Enrollment phase

- Obtain patient informed consent and comply with HIPAA requirements when indicated. Exceptions or 'Waiver of exemption' situations exist when there are

clear links to quality improvement monitoring, such as in the case of cardiovascular device registries.

- Clearly state the following for patients:
    - Research objectives and duration of desired participation
    - How a patient may rescind their participation in this registry
    - Any patient incentives for participation
    - If a patient will be contacted by the research team and under what conditions

Step 3: Participation phase

- Will there be any incentives for continued participation in the registry? If so how will these be administered?

Step 4: End of registry phase

- How will termination of participation be conveyed to the participants? Will there be access to any information or publications that result from the registry?

Chapter 8. Data Collection and Quality Assurance

Overview

This chapter will describe the broad range of processes and technologies for data collection and management and how they are implemented in real-world clinical practice. This chapter will also describe principles of data "cleaning" for registries and may provide examples of registries that exemplify the "gold standard" in terms of thoroughness and comprehensiveness of their validation methods and examples of registries that use less rigorous approaches that are less costly and time-consuming. It will discuss quality standards for systems that collect registry data (e.g. 21 CFR Part11) and the range of methods for assessing the quality of data entered into a registry. It will discuss the cost to benefit tradeoffs inherent in these choices.

Data collection and management

- Possible data sources
    - Structured data collection
        - Questionnaires, Case Report forms, (hard copy, web-based, CATI, PDAs, etc.), public datasets, telephonic/follow up interviews
    - Ancillary systems including:

            - Electronic Medical Records (EMRs) – describe methods of retrieving data from EMRs for incorporation in registries (SQL queries, ETL procedures, etc.); note that EMRs do not typically utilize the same data definitions as might be used in a specific registry
            - Other – some data from ancillary systems may feed into an EMR, other data may not; some systems are stand-alone
    - Data entry methodology
        - Electronic Interfaces – describe process of creating interfaces to electronic data sources (HL-7, Dicom, FTP, sockets, etc.)
        - Online Data Entry – describe alternatives for online data entry (web-based, client-server application, PDA, etc.)
        - Manual Key Entry – describe key-entry systems (double-entry, coding, verification, etc.)
    - Data collection methodology
        - Dedicated data collector vs. data collection by a variety of providers at points of care
            - Qualifications of data collectors and registrars
            - Data collection for multiple registries
        - Adding data from existing sources such as chart abstractions
    - Training required for data collection
        - Training of dedicated data collectors and registrars
        - Training of all providers who might be entering data into the registry
    - Resources required for data collection
        - Cost of electronic infrastructure for data entry
            - Cost of web-based data collection and transmission
            - Cost of hardware and software required for central data collection and data entry at points of care
            - Costs specific to follow up of patient outcomes (e.g. obtaining long term vital status of patients from the National Death Index)
            - Costs and practical issues for utilizing EMRs as source for registry data now and in the future
            - Personnel required and costs associated with them (including training)

Data quality assurance

This section will describe structures, processes, policies, and procedures that need to be put in place to ascertain the quality of the registry as a whole.

- Assurance of data quality, validity, reliability, inter-rater reliability, and security
    - Error sources – clinical error (false positives, false negatives), inter-rater reliability, electronic error (transmission errors, read-after-write), transcription errors (online and key-entry), systemic errors (bias), intentional errors (auditing)
    - Data cleaning – editing, coding, validation
    - Data monitoring – continuous monitoring of variables, looking for abnormal patterns of data (e.g., sudden changes in mean, missing data, etc.)
    - Verifying data
        - What can be done?
            - None
            - Database audits
            - Auditing screening logs
            - Procedures to source data verification
            - Audits: random and for-cause
            - Other options
        - What is being done:
            - Practicality and cost
            - General ranges of what is being done (e.g., ranging from no validation, to 100% source data verification, with a reasonable expectation coming in at about 10%)
            - What is reasonable based on the purpose (safety, clinical and cost effectiveness, quality measurement/improvement, natural history)
    - Data security – storage (access permission control), backup and recovery, archiving, HIPAA privacy, and security issues
    - Assurance of standardization and currency of data definitions
    - Assurance of proper training and maintenance of competencies of data collectors and registrars
    - Assurance of flexibility in data acquisition
    - Assurance of compliance with accrual and other procedures
    - Assurance of the quality (scientific validity and reliability) of the information from the registry (periodic reports, results of observational studies, presentations made at national and public meetings, publications, press releases, etc.)

- Integrity of Registry Authenticity: refer to FDA 21 CFR part 11 regarding electronic records
- Assurance of system integrity and lack of sponsor influence and bias. This would be particularly applicable to any sponsor who maintains a product (i.e. drug or device) registry
- Assurance of the provision of proper resources needed for the maintenance of the quality of data collection and the quality of the registry as a whole
- Assurance of internal/external executive oversight to ascertain (in addition to all of the above):
    - Proper day-to-day management of the registry
    - Periodic monitoring of the outcomes of patients in the registry
    - Adequate determination of cessation of patient enrollment, data collection, and other actions that are necessitated by data analyses from the registry
        - Criteria used to determine when to stop data collection
        - Standard methodologies for collecting and coding data on adverse events in order to meet reporting requirements

Chapter 9. Analysis and Interpretation of Registry Data to Evaluate Outcomes

Overview

This chapter will explain how analysis plans are constructed for registries, how they differ depending on their purpose, and how registry design can affect analysis and interpretation. The chapter will describe analytic techniques that are generally used for registry data and explain how conclusions are drawn from registries and what caveats are appropriate. The chapter will also describe how timelines for data analysis can be built in at the registry's inception and how to determine when the registry data is complete enough to begin analysis.

Issues relating to hypotheses and purpose of registry

- Descriptive vs. comparative
- Pre-specified vs. post hoc
- What is the registry purpose?
    - Clinical effectiveness and comparative effectiveness, including safety as well as natural history, cost-effectiveness, and quality measurement / improvement.

Patient population

- Consider including a flow chart identifying all the stages that need to be quantified. E.g., see AJE 2005: Reporting of Observational Longitudinal Research.
- Inclusion/exclusion
    - Representativeness as relates to purpose
    - Generalizability

Data quality issues

- Are all important covariates collected?
- Data completeness
    - How was missing data handled

Data analysis

- Results should be descriptive, focusing on estimation and precision, not testing
- Are there appropriate time frames and/or constraints for conducting interim analyses?
- How to deal with registries that are changing over time
- How to deal with unanticipated events
- Patient censoring
- Survivor bias
    - Selection bias and means of adjustment (risk, propensity) covered in chapter 4
    - Clustering of patients and means of handling
    - Sensitivity and substudies
    - Evaluating uncertainty

Interpretation of registry data

- Appropriate limitations
    - Historic vs. concurrent controls
- Hypothesis generating, not testing
- Feedback loop to design of registry
- Feedback to data safety and monitoring board

Examples of analysis (case studies)

- Descriptive/utilization studies

- Drug/device safety studies
- Treatment/effectiveness comparisons
- Quality assessment/quality improvement

SECTION III. EVALUATING A REGISTRY

The goal of this section is to provide the public and the government with information with which scientists and stakeholders can evaluate the quality of a registry.

This section will review several of the areas described in the registry design section which have an impact on the quality of a registry. Although the registry design and evaluation sections will share common themes and concepts, the level of detail and tone will differ between the two sections. As an example, the design section will provide more information about why certain registry features are important, but the evaluation section will focus on explaining how to determine whether these features have been incorporated into a specific registry and whether they are adequate to ensure the validity and reliability of the registry data.

This section will also feature several case studies of registries that have met their objectives as well as case studies of registries where their limitations exceeded their strengths. It will describe the key reasons for their effectiveness or lack of success.

Chapter 10. Evaluating Registries

Overview

This chapter will provide a list of key questions to guide the evaluation of a registry design and guidance about the most appropriate answers to these questions and provide readers with a tool for rating a registry on these key elements. This chapter will include information that can be used for evaluating or auditing the integrity of a data system and will provide principles for assessing the quality management system surrounding the operation of a registry based on its intended purpose. This chapter will provide specific guidance for assessing registry data quality and will propose certain standardized characteristics of registries that should be reported with registry data to allow the reviewer to assess the quality of the data presented. The chapter will also provide guidance for evaluating the interpretation of registry data.

Why evaluate registries?

This section will address the following questions:

- What is the most appropriate way to use data from registries?

- Is the data from this registry strong enough (valid and reliable) to accurately assess patient outcomes and make important decisions about treatment and coverage?
- What can be done to improve registry design, operations, and analysis and use so that it meets the standards for being sufficient for the intended purpose?

What caveats should be kept in mind when interpreting data from registries?

Evaluating registries in the context of their intended purpose

This section will differentiate the level of rigor required of a registry's design and operation based on its intended use. Its main theme will be that the purpose of the registry will guide the strength of data needed to support the purpose. For example, registries that are used for major decision-making, such as assessing safety, clinical and cost effectiveness, and compliance with regulatory agency requirements, require a high level of rigor whereas registries that are used primarily for enumeration, description of the natural history of disease, and/or patient management may be very informative, even without the same level of rigor as those used for safety-type studies.

Critical Appraisal Tool & Guide for Evaluating Registries

This section will present a tool that will help readers to describe and differentiate best practices for registry design and operations from minimal acceptable practices, as well as from those practices that are not acceptable.

A minimum useful set of descriptive information will be created, as well as information that can be used for evaluating registries in the context of the purpose for which they are conducted and the rigor with which they provide sound evidence. Information that can be used to guide evaluation is described in the context of:

- Best practice
- Necessary practice for purpose
- Desirable but not necessary
- Below sufficient quality to achieve purpose
- Not Applicable

The chapter may also describe the following:

- Implications of meeting (or missing) the threshold to be considered "best practice"
- What can be done to strengthen registries, e.g., external validation, alternative controls, re-analysis
- This information will be determined based on contributions from individual chapters. Examples of what types of information might be provided include:

- For evaluating registry design
    - Recruitment information and comparison of participating and non-participating patients, providers, and research sites
    - Assessment of registry oversight and governance: Was informed consent necessary, and if so, was it obtained? Was Institutional Review used at each site, and if not, why not?
- For evaluating the quality and security of registry data systems
    - Information for evaluating and auditing the integrity of a data system (including standards such as 21 CFR and HIPAA security standards)
    - Information for evaluating participant protections: the informed consent process, the informed consent document, privacy and confidentiality violations, OHRP and HIPAA regulatory compliance
    - Questions that can be used to determine whether a registry that provides patient-specific feedback to providers has the appropriate safeguards for privacy, as contrasted with registries that only provide aggregate, summary information to a central reviewer
- For evaluating the quality of registry data, analysis, and interpretation
    - Desirability of using validated tools (e.g., for patient-reported outcomes) and standardized data collection tools, where possible, to enhance validity and reliability
    - Commonly used data validation methods and checks for internal consistency
    - Is there information about how the data were collected and validated and how errors were identified and corrected?
    - What procedures were applied to drop-outs and those lost-to-follow-up in registries with prospective follow-up?
    - Was the analysis appropriate for observational data?
    - Was adequate information provided to determine whether the analysis was appropriate to support the interpretations given?
    - Did the interpretation of the data consider the potential sources of bias and generalizability of the inference?
    - Balancing feasibility and cost effectiveness